REMARKS

Claims 1, 7, 10-11, 33-36, 39, 41, and 43-44 were pending in the present application. Claims 34-36 are canceled herein. Claims 1, 7, 10-11, 33, 36, 39, 41, and 43-44 are pending. No new matter is added thereby. Claims 1 and 41 are amended herein to correct minor typographical errors. In view of the foregoing amendments and arguments that follow, Applicant requests withdrawal of all rejections upon reconsideration.

Priority

Preliminarily, Applicant notes with appreciation the Office's acknowledgement that the claims are entitled to the filing date of the GB priority application making the effective filing date of the present claims April 24, 2001 as well as the Office's withdrawal of the rejection of claims 1, 7, 10-11, 33, 39, and 41 for failing to comply with the written description requirement.

Rejection Under 35 U.S.C. 112, first paragraph: Enablement

Claims 1, 7, 10-11, 33, 39, 43, and 44 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. This rejection is, essentially, a rejection for over-breadth. The Office's view is that Applicant has not enabled his invention throughout its scope. Specifically, the Office asserts that Applicant has not enabled a method for producing single chain antibody in any other nonhuman mammal other than a mouse and using a naturally occurring VHH locus other than that of a llama. For the reasons set forth below, Applicant traverses this rejection.

Preliminarily, Applicant notes the glaring absence in the Office's discussion of the three declarations previously submitted by Applicant – i.e., the declarations of Drs. Weiner,

Grosschedl, and Grosveld. These declarations addressed many of the enablement issues that the Office continues to rehash over and over again regarding the use of all non-human mammals – e.g., competition between the transgenic and endogenous loci, serum concentration, and use of ES cells. The Office's lack of discussion of these declarations suggests that, contrary to legal precedent and the MPEP, the Office is not considering them. The Office repeatedly notes the lack of evidence, while disregarding these declarations. This is clear error on the Office's part.

> Applicant may submit factual affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement. *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"); *cf. In re Alton, 76* F.3d 1168, 1174, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996) (declarations relating to the written description requirement should have been considered).

MPEP § 2164.05, emphasis in original. Applicant maintains that, when all the evidence is properly considered, Applicants claims are enabled.

> The examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should **never** make the determination based on personal opinion. The determination should always be based on the weight of all the evidence.

Id., emphasis in original.

The passage from Murray cited by the Office does not evidence lack of enablement. First, Murray regards the modification of livestock, not their use for producing proteins. Second, that the constructs have to be tested in the species of interest is not fatal to enablement -- all

experimentation is not precluded, just undue experimentation.

> The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

MPEP § 2164.01.

Additionally, the Office has raised new issues that are suspect considering the point in prosecution, if not completely irrelevant to Applicant's invention. The Office raises, for the first time, the issue of glycosylation. As the Office is no doubt aware, glycosylation does not affect the ability of the antibody to bind antigen. Indeed, the Lillico reference the Office raises discusses the **potential rejection** of antibodies carrying certain oligosaccharides from other mammals in humans, not the non-functionality of such antibodies. Applicant fails to see the relevance of this line of argument by the Office, other than to further protract prosecution unnecessarily.

The Office also raises, for the first time, the issue of allelic exclusion, asserting that allelic exclusion only exists in humans and mice. The Office cites no evidentiary support for its assertion that allelic exclusion only exists in humans and mice. This is error. See MPEP § 2164.05, *supra.* Indeed, the evidence is to the contrary. Although the mechanisms may be different, there is allelic exclusion in other species of animals. See, for example, Weill and Reynaud (1998) *Dev. and Comparative Immunology*, 22, 379-385; Weill et al. (2002) *seminars in Immunology* 14, 213-215; and William Paul (2008) Fundamental Immunology Chapter 7 (in particular, page 40-43) **(copies enclosed)**.

Regardless, others have published on the expression of human or humanised

immunoglobulin heavy chain transgenes in chickens and rabbits (see WO 02/12437 A2) and cattle (Kuroiwa et al (2002) Nature Biotech. 20 889-894 (submitted previously), see also WO 02/070648 A2 and WO 03/097812 A2), each leading to the productive expression of the transgene encoded immunoglobulin. These publications teach the successful production of transgenic animals expressing human or humanised immunoglobulin genes in diverse animal species. There is no uncertainty; the methodology is provided, and antibodies are produced. In each situation the species in question is intended to be used as a factory to produced antigen specific human or humanised antibodies for use as reagents and medicines. Whatever the precise mechanism of allelic exclusion which differentiates rodent and primates from other species, typified by the rabbit, cattle and chicken, an immunoglobulin heavy chain transgene can be recognised and treated as an allele in all species. The precise mechanisms of allelic exclusion have no relevance with respect to the implementation of the invention under examination.

The Office also raises, for the first time, the use of VHH sequences from species other than llama. Incredibly, the Office states that "[a]bsent of evidence to the contrary, it is not clear that any other naturally occurring VHH coding sequence of any other specie would be functional in other species of nonhuman mammal . . ." (Office Action, p. 10). The Office has apparently forgotten that the burden is on the Office to show why another naturally occurring VHH coding sequence would not be functional, not on Applicant to show that it would be functional. MPEP § 264.04. The Office has not done so.

Finally, the Office again focuses upon serum levels of immunoglobulin (Office Action, page 7), even though this issue was addressed by Drs. Weiner and Grosveld in their declarations

(see Declaration of Louis M. Weiner, M.D., ¶ 20, and Declaration of Dr. Frank Grosveld, ¶ 5). It is not necessary that there be high levels of the immunoglobulin in the serum. Indeed, Applicant previously amended the claims to remove the requirement that the antibody be isolated directly from the mammal.

Applicant requests that this rejection be withdrawn.

Rejection Under 35 U.S.C. 112, second paragraph

Claims 34-36 were rejected as allegedly indefinite for depending upon a canceled claim. Claims 34-36 have been canceled. This rejection has been obviated by amendment.

Rejection Under 35 U.S.C. 103(a)

Claims 1, 7, 10-11, 39, 41, and 43 were rejected as allegedly obvious over Surani et al., Lonberg et al, Nguyen et al., and NCBI Accession No. AF305944. Applicant traverses.

This rejection is a clear example of the inappropriate use of hindsight, which is still disfavored. "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR Int'l Co. v. Teleflex, Inc.,* 550 U.S. 398, 421 (2007) (citing *Graham*, 383 U.S. at 36). As the Court of Appeals for the Federal Circuit recently reemphasized, a flexible teaching, suggestion, motivation test is the "primary guarantor against a non-statutory hindsight analysis." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). The Office's only motivation cited is the need to enlarge the antigen-binding repertoire of HCAb. The Office cites no source for this motivation. The Office's proposed motivation is clearly an example of "*ex post* reasoning."

The Office then relies upon what it was taught by Applicant – i.e., that eliminating the

function of CH1 is sufficient to facilitate formation of HCAb – to combine Nguyen et al. with Surani et al., Lonberg et al., and NCBI Accession No. AF305944. Such use of hindsight is inappropriate. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention.")

Nor can it be argued there was a reasonable expectation of success. It was not known as of the effective filing date, and is still not known now, whether camelid heavy chain-only antibodies are generated in the same B-cells as regular tetrameric camelid antibodies comprising heavy and light chains, or whether camelid heavy chain-only antibodies are produced in a specialized class of camelid B-cells (see Zou et al (2005) J.Immunol. 175, 3769-3779, forwarded previously with Declaration of Louis M. Weiner, M.D., for post-filing discussion of the uncertainties regarding the process of heavy chain only antibody expression in camelids. Moreover, Zou et al. raise a fundamental issue (see p3769 right hand column) as to how individual HCAbs alone, in the absence of light chain can "facilitate B cell differentiation to mature and specialised stage." Further, in Nguyen et al., (2003) *Immunology*, 109: 93-101 **(copy enclosed**, the very same Nguyen on the reference cited by the Office), the authors express surprise that mouse myeloma cells even have the capability of expressing an already rearranged camelid heavy chain only antibody gene. Both of these papers were published several years after Applicant's priority date.

Claim 33 was rejected as allegedly obvious over Surani et al., Lonberg et al, Nguyen et al. and NCBI Accession No. AF305944, further in view of O'Keefe et al. The deficiencies of the

foregoing references are discussed above, discussion incorporated herein. O'Keefe et al. does not overcome these deficiencies.

Claim 44 was rejected as allegedly obvious over Surani et al., Lonberg et al, Nguyen et al. and NCBI Accession No. AF305944, further in view of Davies et al. The deficiencies of the foregoing references are discussed above, discussion incorporated herein. Davies et al. does not overcome these deficiencies.

Applicant requests that these rejections be withdrawn.

Applicant reserves the right to address the art considered pertinent to Applicant's disclosure at such time as it is used in a rejection.

CONCLUSION

Applicant respectfully submits that claims 2, 7, 10-11, 33, 39, 41, and 43-44 are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 665-5593, if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,

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